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Intensity modulated radiotherapy (IMRT) for pediatric cancer patients: The advantage and fear of second malignant neoplasm

Mohamed S. Zaghloul *

Radiotherapy Department, Children's Cancer Hospital, Egypt and National Cancer Institute, Cairo University, Egypt

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Abstract Intensity-modulated radiotherapy is used for delivering more efficient homogenous dose to the target and lowering of dose to the surrounding normal tissues. However, a second malignant neoplasm may develop after prolonged latent period. The use of modern precise radiotherapy techniques in the pediatric age group has many controversial issues in spite of its proven dosimetric distribution advantages and the considerable decrease of normal tissue complication probability (NTCP). This concern is due to many factors; mainly the exposure of a larger volume of normal tissues to low dose radiotherapy. Children have more proliferating tissues compared to the adults. However, the epidemiological data did not detect an increase in the incidence of radiation-induced second malignancy. This issue is still controversial as IMRT and other precise radiotherapy techniques were not widely used except recently. This may entail a thorough careful follow up for children treated with these techniques to detect any incidence increase.

The incorporation of local radiotherapy with extensive chemotherapy and autologous stem cell transplant in the treatment of high risk neuroblastoma (NB) had led to excellent local control rates exceeding 80% [1]. Abdominal NB is often located in the midline and paraspinal region encroaching on one or both kidneys. The recommended radiation dose is in the range of 21–36 Gy depending on the presence of residual tumors post surgical excision. With the conventional 3 dimensional conformal radiotherapy (3DCRT) the dose received by the kidney(s) may exceed its tolerance. Adding to this, the situation in NB is more complicated by the administration of nephrotoxic chemotherapy mainly cisplatin. For more efficient homogenous dose to the target and lowering of dose to the kidneys, Nazmy and Khafaga [2] used the intensity modulated radiotherapy (IMRT) in 13 NB children after autologous stem cell transplant. Their results showed good survival rates without late complications (skeletal asymmetry or second malignancy) at a median of 26 months post IMRT. Although this

* Address: Radiation Oncology Department, Children's Cancer Hospital & National Cancer Institute, Cairo University, Cairo, Egypt. Tel.: +20 10017 20664; fax: +20 2 23619036.
E-mail address: mszagh@yahoo.com

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interval is short for the detection of survival advantage and to rule out such complications, yet they could illustrate a clear dosimetric advantage of IMRT in the kidneys, liver and vertebrae compared to 3DCRT. Hillbrand et al. [3] showed earlier in a dosimetric study that volumes of the kidneys and liver irradiated at the level of the tolerance dose were decreased by 65% and 75% respectively for abdominal NB patients treated with IMRT.

The use of modern precise radiotherapy techniques including IMRT, volumetric modulated arc radiotherapy (VMAT), helical tomotherapy (HT) and extracranial stereotactic radiotherapy in the pediatric age group has many controversial issues in spite of its proven dosimetric distribution advantages. The more homogenous dose to the target volume with much lesser dose to the surrounding organs at risk (OAR) definitely leads to a considerable decrease of normal tissue complication probability (NTCP). The potential of development of radiation-induced second malignant neoplasm (SMN) is a major concern in such group of patients. This concern is due to many factors. The most important one is the exposure of a larger volume of normal tissues to low dose (peripheral dose) radiotherapy. Children are a major concern as they have more proliferating tissues with more numbers of stem cells compared to the adults. Furthermore, promotion of growth hormones to tissue is likely to be greater during young age [4]. Hall and Wuu [5] hypothesized the increase of SMN in patients 10 years after IMRT by 0.75% (from 1% after conventional to 1.75% after IMRT) depending upon a hypothetical mathematical model. More monitor units are used to deliver IMRT than 3DCRT to deliver the same dose which may translate into more radiation leakage to different organs at risk and to the entire patient body. It is well known that the delay between irradiation and emergence of SMN is seldom be less than 10 years. This delay may cause a considerable under- or over-estimation, unless actuarial cumulative incidence is computed [4]. Moderate or high doses of radiation with the resulting cell kill effect disorganize the tissues and lower the efficacy of proliferation control of the mutated cells to develop manifest cancer [6].

Epidemiological data did not detect cancer excess in children where a dose below 100 mGy is delivered at a high dose rate or 200 mGy delivered at a low dose rate [7]. The extrapolation of the mathematical models to real patients is still of dubious validity and needs confirmatory revision. The fear expressed by some radiobiological researchers [8–10] that precise radiotherapy including IMRT, HT, VART may increase the incidence of SMN through increasing the volume of normal tissues receiving low dose is a subject for extensive debate and controversy. This low dose is primarily caused by a leakage through the accelerator head, jaws and multileaf collimator (MLC) together with the internal scatter within the patient. Secondary radiation from MLCs contributes a significant portion of low dose in IMRT plans [11]. Athar and Paganetti [12] estimated that children and young patients showed significantly higher risk than adults and deep seated tumors are associated with an elevated risk of radiation-induced SMN than shallow treatment fields. They estimated further the uncertainty in their suggested model to be in the range of 50%. This risk is usually related to the integral dose or low dose volume. The integral dose equals to the mean dose multiplied by the volume of each structure. The low dose volume is defined as the volume receiving a total dose of 2 Gy or more. Tubiana [4] in his review showed that second primary malignancies are observed for in-field organs receiving doses in excess of 2 Gy. The IMRT had higher integral dose than 3DCRT in some studies [13,14] and others reported a decrease [15,16], while some others reported mixed results for different sites when comparing the non-tumor integral dose with IMRT and HT [17]. Yang et al. [18] reported that in spite of the increase of the volume of normal tissues receiving low dose yet, the integral doses to the normal tissues did not increase with IMRT or HT compared to 3DCRT. In the contrary, they discovered that the integral doses of the normal tissues and the whole body were significantly lower with IMRT. Specifically, Aoyama et al. [15] reported that IMRT and HT resulted in 5% and 4% lower integral dose to normal tissue, respectively. On the contrary, Lian et al. [13] reported a significant increase in the integral dose of normal tissues with IMRT and HT compared to 3DCRT. This discrepancy in the 2 studies was probably due to the larger volume ratio of the normal tissues to PTV in Lian et al. study. The volume of peripheral dose or low dose depends on the technical equipments, technology and on the inverse planning and segmentation algorithms used. Therefore, the peripheral dose may vary in the pre IMRT era than in recent days [19]. Salz et al. [19] measured the peripheral dose for a 4-year old child irradiated for brain tumor using IMRT and 3DCRT. The measurements showed an increase of the peripheral dose in IMRT measuring 9 mGy; a dose similar to the dose of CT scan or the dose of a verification film shot with a monitor unit.

In conclusion, IMRT has to be used in children whenever necessary and when it is needed together with activating the extended and prolonged follow up programs in order to detect any actual increase in the SMN and correlate it to the possible hazard factors. On the other hand, the usage of treatment plans and algorithms with less monitor units should be encouraged to avoid part of the dose outside the targets. Furthermore, changes in the hardware of the machines (linear accelerators, HT, Cyberknife) can reduce the peripheral dose. It was reported that flattening filter-free beams in IMRT reduce the head scatter dose down to 52% in 6 MV and 65% in 10 MV photons [20].

Conflict of interest

None declared.

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